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Title:

The Influence of Socioeconomic Deprivation on Outcomes in Pancreas Transplantation in England; Registry Data Analysis

Authors:

Argiris Asderakis, MD[1]; Usman, Khalid, PhD[1]; Susanna Madden;[2] Colin Dayan, PhD[3]

Affiliation:

[1]Cardiff Transplant Unit, University Hospital of Wales, Heath Park, Cardiff, CF14 4XW, UK.

[2]Statistics and Clinical Studies, NHS Blood and Transplant, Fox Den Road, Bristol, BS34 8RR, UK.

[3]Cardiff University, University Hospital of Wales, Cardiff, CF14 4XW, UK.

Correspondence author details:

Name: Mr Argiris Asderakis

Email: argirisasd@me.com

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Abbreviations:

EIMD	English Index of Multiple Deprivation
SPK	Simultaneous Pancreas and Kidney
PTA	Pancreas Transplant Alone
PAK	Pancreas After Kidney
CIT	Cold Ischemic Time
DBD	Donation after Brainstem Death
DCD	Donation after Cardiac Death
LD	Living Donor
WIMD	Welsh Index of Multiple Deprivation

ABSTRACT:

Socioeconomic deprivation is associated with poorer outcomes in chronic diseases. The aim of this study was to investigate the effect of socioeconomic deprivation on outcomes following pancreas transplantation among patients transplanted in England. We included all 1270 pancreas recipients transplanted between 2004 and 2012. We used the English Index of Multiple Deprivation (EIMD) score to assess the influence of socioeconomic deprivation on patient and pancreas graft survival. Higher scores mean higher deprivation status. Median EIMD score was 18.8, 17.7 and 18.1 in patients who received SPK, PAK and PTA respectively (p=0.56). Pancreas graft (censored for death) survival was dependent on the donor age (p=0.08), CIT (p=0.0001), the type of pancreas graft (SPK vs. PAK or PTA, p=0.0001), and EIMD score (p=0.02). The 5-year pancreas graft survival of the most deprived patient quartile was 62% compared to 75% among the least deprived (p=0.013),

and it was especially evident in the SPK group. EIMD score also correlated with patient survival (p=0.05). Looking at the impact of individual domains of deprivation, ‘Environment’ (p=0.037) and ‘Health and Disability’ (p=0.035) domains had significant impact on pancreas graft survival. Socioeconomic deprivation, as expressed by the EIMD is an independent factor for pancreas graft and patient survival.

Introduction:

Socioeconomic deprivation is an important factor in determining poor health and reduced survival (1, 2). There is evidence that the prevalence of chronic diseases including ischaemic heart disease, diabetes and renal failure is higher and the outcomes of treatments is poorer for patients living in more socioeconomically deprived areas (3-6). Access and referral to specialist services may be delayed for patients from socioeconomically deprived areas in comparison to patients from less deprived areas (7-9).

Specifically in transplantation, several studies from the United States and in the UK have shown poorer outcomes in terms of graft survival and rejection episodes following renal transplantation in the most socioeconomically deprived patients (10-15). There is also evidence to suggest that socially deprived patients have reduced access to deceased donor kidney transplantation and also a lower probability of a living donor transplant (7, 16, 17).

Type 2 but not type 1 Diabetes has been shown to be more prevalent in patients who live in more deprived areas, probably due to an increased exposure to factors which cause diabetes (6). In addition to this, several studies have shown that diabetes-related mortality is associated with deprivation (18, 19). Main mechanisms proposed to influence this relation are health behaviours, access to care, and processes of care, sometimes referred to as proximal mediators/moderators (20).

By using the Welsh Index of Multiple Deprivation we have not been able to demonstrate differences in outcomes following pancreas transplantation in Wales in relation to socioeconomic deprivation (21). Therefore the necessity arose to study the influence of deprivation on outcomes following pancreas transplantation on a larger scale.

The aim of this study was to investigate the effect of socioeconomic deprivation on outcomes following pancreas transplantation among patients transplanted in England. In addition, given the availability of detailed data, and the numbers involved, we set to correlate outcomes to specific domains of socioeconomic deprivation.

Patients and Methods:

Patient Population:

All patients who underwent a pancreas transplant (simultaneous pancreas and kidney, pancreas alone, or pancreas after kidney) between December 2004 and December 2012 were identified from a prospectively updated and maintained database held in the UK national organization for donation and transplantation (NHS BT).

Demographic data were collected on the donors (age, gender, cause of death, warm and cold ischaemic time, donor BMI) and recipients (age, gender, duration of diabetes, associated renal failure, any previous transplants), HLA-DR mismatch and duration of follow up. The primary outcomes were defined as patient and pancreas graft survival. Secondary outcome related to kidney graft survival when this kidney was transplanted as part of an SPK. Graft survival dates were censored for death and failure date for the pancreas graft was defined as the day of re-commencement of insulin or other anti-diabetic medication (if this was for longer than 14 days). In cases where the graft has been reported at any time as ‘not failed’ but no assessment date has been provided to NHS BT, survival time could not be calculated and therefore these cases were excluded from the survival analysis (16 cases).

Calculation of deprivation scores:

Deprivation scores were calculated using the English Index of Multiple Indices of Deprivation (EIMD) 2010. The Indices of Deprivation is based on the concept that deprivation consists of more than just poverty. This is a collective score derived by 38 separate indicators grouped in seven domains: Income, Employment, Health and Disability, Education, Community safety (crime), Geographical access to services, Living Environment (22). Scores are calculated for each domain separately and represent a number for each geographical area and postcode within England. A higher score signifies the area with a higher proportion of people who are classed as deprived and a lower score signifies an area with a lower proportion of deprivation. Each domain is given a weighting and the aggregation of those weighted domains provides the overall EIMD score. We should stress that EIMD is a community based score. A person living in an area with a higher score (that signifies this area has a higher proportion of people who are classed as deprived) might be more or less deprived based on an individual based score. Table 1 shows the domains, the factors that contribute to the scoring within each domain, and the weighting given.

For the purpose of the study English recipients have been defined as English by their residential postcode but they may have, rarely, been transplanted in Wales or Scotland.

Statistical Analysis:

EIMD data were analysed as absolute numbers and in quartiles with quartile (group 1) being the least deprived and quartile 4 (group 4) being the most deprived. All data analysis was carried out using SPSS version 23. Chi squared test for association was used to analyse the observed and expected frequencies and a p-value of <0.05 was used for any differences deemed to be significant.

Pancreas graft survival times were censored for death and pancreas graft failure dates were defined as the date for re-commencement of anti-diabetic/insulin therapy (if this continued for over 14 days). Graft survival of kidneys in SPK patients were censored for death and calculated to the date of starting renal replacement treatment or re-transplantation of kidney. Cumulative survival was calculated using the Kaplan-Meier life table method and differences in survival between groups of patients were analysed by the log rank method. A Cox proportional hazards risk-adjusted regression model was used to estimate the influence of individual domains of deprivation along with more 'traditional' risk factors to the outcome of pancreas transplantation.

RESULTS:

Patient demographics

A total of 1270 patients underwent pancreas transplantation in England between December 2004 and December 2012. Of the 1270 transplants, 1259 had full demographic and deprivation data and were included in the analysis 1017 (80.8%) were simultaneous pancreas and kidney (SPK), 109 (8.7%) were pancreas alone (PTA), and 133 (10.6%) pancreas after kidney (PAK). One thousand and sixty-eight patients (84.8%) patients received the organs from a donor after brain-stem death (DBD) and 191 (15.2%) from a donor after circulatory death (DCD). Fifty patients (4%) had received a previous pancreas transplant prior to this incident transplant. There were proportionally more male recipients in increasingly deprived areas. Details of the patient demographics are described in Table 2. None of the patients were lost to follow up and the minimum follow up was 2 years and 3 months (median 5 years 2 months).

Deprivation scores

Details of the deprivation scores for each of the domains are shown in Table 3 for the least and the most deprived groups. The median overall score of patients who had pancreas transplants was 18.48 (range 1.06 - 87.8), whereas the median overall score for the total population of the area served by the transplant units involved was 17.25 (range 0.8 – 87.8).

The median EIMID score was the same in patients who received SPK (18.8) compared to patients who received PAK (17.7) or PTA (18.1), (x^2 test, p=0.56). (Data for the SPK and PAK groups is depicted in Figure 1).

Pancreas graft survival

Five-year censored for death pancreas graft survival in the most deprived quartile group of recipients was 62% compared to 75% among those comprising the least deprived quartile group (Log rank test, p=0.013) (Figure 2). When analysing the SPK patients alone (who comprised the large majority of pancreas transplants) the same trend was seen, with 66% pancreas 5-year graft survival in the most deprived compared with 81% in the least deprived group (Log rank test, p=0.016) (Figure 3).

A multivariable Cox regression analysis found that the pancreas graft survival during this period was dependent on: Donor age (p=0.08), CIT (p=0.0001), type of Pancreas graft (SPK vs. PAK or PTA) (p=0.0001), and socioeconomic deprivation as expressed by the EIMD score (p=0.02). When SPK patients were analysed separately donor age (p=0.04), CIT (p=0.006), and social deprivation as expressed by the EIMD score (p=0.005) were the ones significantly affecting pancreas graft survival. Among the rest of pancreas transplants types (PAK or PTA) only CIT remained significant for pancreas graft survival (p=0.05). There was some separation of the 5-year survival according to the highest vs. the lowest quartiles of EIMD scores (51% vs. 44%) but the difference was not statistically significant (p=0.2).

Patient Survival

Multivariable regression analysis indicated that patient survival was affected by the donor age (p=0.046) recipient age (p=0.009), and the EIMD group (lowest quartile vs. highest quartile, p=0.01) [graph 4].

Analysis of pancreas graft survival, *without censoring for death with a functioning graft,* showed that the EIMD group affected (as expected given the previous results on patient survival and censored graft survival) significantly this outcome (lowest quartile vs. highest quartile, p=0.008).

Kidney Graft survival

Among SPK patients, kidney graft survival was associated with deprivation scores but not on a clear linear pattern. The lowest deprivation quartile, according to EIMD score, had higher 5-year kidney survival compared to the two quartiles of higher deprivation (91% vs. 83%, x^2 test, p=0.014).

Domains of deprivation

It is difficult to separate the effect of deprivation domains given that there is, as expected, significant overlapping. There is a strong correlation between individual domains scores (data not presented).

When looking at separate deprivation domains in univariate analysis, pancreas graft survival was negatively affected by higher deprivation score in the Income (p=0.05), Health and Disability (p=0.007) and Environment (0.008) domain, but not in the rest of the domains.

When significant factors from the univariate analysis were inserted in a Cox regression model, CIT of less than 12h compared to over 12h (p=0.001), SPK vs. PAK or PTA (p=0.0001), Environment deprivation score group (p=0.037), Health and Disability (p=0.035), and [marginally] donor age (p=0.09) had significant impact on pancreas survival whereas Income deprivation score group did not.

When separate Cox regression analysis was performed for SPK only transplants, donor age (p=0.047), CIT (p=0.01) and Health and Disability domain deprivation score (p=0.003) were the factors significantly affecting pancreas graft survival.

DISCUSSION:

This study, that includes all patients in England who received a pancreas transplant over 8 years, demonstrates a strong association between socioeconomic deprivation and survival following pancreas transplantation. A higher rate of patient death is common in this study with a series of studies on other chronic health conditions, which could be possibly attributed to the impact of deprivation on the disease rather than on the intervention. It is very interesting but also particularly worrying to see that pancreas graft survival, when censored for death, is also associated with social deprivation. The explanation for this is rather complex. In a universal health system free at the point of delivery as in UK, it cannot be simply explained by limited access to services or required medication.

Although increased acute rejection among the more socially deprived was one of the factors identified in a Welsh study in kidney transplantation as contributing to a similar association (10) we did not have uniform information in biopsy proven rejections as part of the current study.

To date, this is the first study powered to evaluate the influence of socioeconomic deprivation on outcomes following pancreas transplantation. Several studies from the UK and the US have studied the influence of deprivation on outcomes following kidney transplantation. Although one study from the UK (based in the West of Scotland) reported that social deprivation had no effect on outcomes from kidney transplantation (23), the majority of previous studies in this area have reported a negative impact of deprivation on outcomes (10-15). A study that evaluated the influence of deprivation on outcomes following kidney transplantation from Wales, showed significantly higher rates of acute rejection amongst the most socioeconomically deprived patients, and income deprivation to be an independent predictor of graft survival (10). A similar study on pancreas transplant patients transplanted in Wales was unable to demonstrate a difference in survival or acute rejection (biopsy proven pancreas rejection data was available) according to socioeconomic deprivation as measured by the Welsh Index of Multiple Deprivation (21). This study was not powered to detect differences but there was not any obvious trend detected either. The Welsh Index of Multiple deprivation is not directly comparable with the English Index we used in the current study. Housing and Access to services are separate domains in the Welsh index, and the weighting of domains differs slightly but the underlying principles of the two indexes are broadly similar.

A common criticism of similar studies is that they are compromised by known socioeconomic discrepancies in the referral for transplantation, where patients with lower socioeconomic status are less frequently referred. This could be a potentially large confounder of the study.

Ideally a study would first investigate social deprivation and referral followed by social deprivation and outcomes.

A surrogate measurement of that, in type I diabetics with kidney failure, is access to living donation. There is some evidence to suggest that socially deprived patients have a lower probability of having a living donor transplant (7, 16, 17). Although other factors such as co-morbidities may play a role in the choice of the modality of transplantation in type I diabetics with renal failure (SPK vs. LD followed by PAK), it is interesting to see that in this study PAK patients (normally the ones that had access to a living donor) had the same overall deprivation score with SPK patients. Whether the small numerical difference seen in EIMD scores would have been higher, if more PAK patients were available to study, is difficult to say. It is also difficult to analyse separately domains of deprivation within the PAK and PTA groups due to the number of patients at risk.

A limitation of this study is that it is not a randomized controlled trial and suffers from the inherent problems associated with registry data analysis. However, a randomized controlled trial in this area is impossible and although the analysis of the data was performed retrospectively, the data was collected and maintained prospectively by the UK national transplant organisation. In addition EIMD as well its Welsh equivalent, (the WIMD), gives an area based deprivation score, i.e. each individual is given a score based on the degree of deprivation of their local community. A person living in an area with a higher score (that signifies this area has a higher proportion of people who are classed as deprived) might be more or less deprived based on an individual based score. It is unlikely that all residents of a specific area will have the attributes of that community. However, it has been shown that in the absence of individual based data, area based data are reasonable proxies (24-26). It is rather important finding that community based deprivation affects the outcome following such a specialized intervention. The strong correlation among the individual domain scores is supportive of that notion. Our intention to obtain, even limited personal financial information with consent, was frowned upon by ethics committee.

In this study there is complete follow up data with a median follow up over 5 years. This shows the strength of the NHS BT registry in UK and the commitment of the transplant centres to providing data. In the 16 patients where the graft has been reported at any time as ‘not failed’ but no assessment date has been provided to NHS BT, survival time could not be calculated and therefore these cases were excluded from the final survival analysis.

A major strength of this study is that, due to the numbers involved, a domain sub-analysis was possible and appropriate. The overlapping of domains cannot be over-emphasised so certain domains might be also proxies for other deprivation factors. It is interesting to see though that both the Environment and Health and Disability domains were significant factors for pancreas graft outcome.

The Education domain did not affect outcome. In an earlier study by Robinson et al. there was a 4 times higher mortality for type I diabetics who left school before 16 years of age compared to those who left school at or after 16 years of age (19).

The Environment domain results were interesting. This domain includes air quality and emissions, proximity to refuge and industrial sites, patients living in areas with poor air quality and closer to industrial sites being classified as more deprived for this domain. It might indicate that urban deprived areas’ population fares worse than other deprived areas in the context of transplantation. It is worth mentioning that a study on diabetic patients from deprived English inner city locations had shown less intensive insulin treatment and more hypoglycaemia among those patients (27).

In addition, our current study should be seen in the context of wider UK mortality trends. A recent UK study on the impact of the North South divide showed that for 25–34 and 35–44 age groups, from 2010 to 2015 the rate of decline in premature mortality plateaued, and northern excess mortality increased sharply between 1995 and 2015 (28). The North of England is where city deprivation has persisted even at times of relative UK development echoing findings about the impact of Environment deprivation domain in the current study. The effect of persistent deprivation on a young diabetic group might have been particularly pronounced.

In conclusion, the study has shown significant differences in outcomes following pancreas transplantation in England in relation to socioeconomic deprivation. Targeted approaches to the more deprived population might reduce the significant penalty of graft survival seen in patients from the most deprived areas. But this might not be enough. This study also emphasizes the importance of addressing social inequality as a means of achieving better health outcomes even in areas of rather complex interventions as transplantation.

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Author contributions:

AA: conceived the study design performed the analysis, interpretation of results and writing of the manuscript.

UK: participated in the writing of the manuscript

SM: provided the data on behalf of the NHS BT, gave statistical advice at the start of the project, edited the manuscript

CD: edited the manuscript

Funding: N/A

DISCLOSURE:

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure Legends

Figure 1: Comparison of EIMD scores for SPK (median 18.8) vs. PAK patients (median 17.7, p=0.56) shows that they are not different.

Figure 2: Kaplan-Meier estimates of pancreas graft survival in the four quartiles of deprivation as calculated by EIMD scores. The group 1 had 75% 5-year pancreas survival compared to 62% survival of group 4 (p=0.013).

Group 1 least deprived quartile, Group 4 most deprived.

Figure 3: Kaplan-Meier estimates of pancreas graft survival of the SPK only recipients in the four quartiles of deprivation as calculated by EIMD scores. The group 1 had 81% 5-year pancreas survival compared to 66% survival of group 4 (p=0.013).

Group 1 least deprived quartile, Group 4 most deprived.

Figure 4: The patient survival of pancreas transplant recipients of the lowest quartile of deprivation according to EIMD scores is significantly higher than the one of those in the higher deprivation quartile (Cox regression, p=0.01).

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Tables and Figures:

Table 1: A summary of the components of the English Index of Multiple Indices of Deprivation (EIMD) 2010

Domain	**Specific Indicators used to calculate the score**	**Weighting given to overall score (%)**
Income	Proportion of population receiving income-related benefits	22.5
Employment	Proportion of working age residents receiving employment-related benefits	22.5
Health and disability	Standardised all-cause death rate, cancer incidence, low birth weight and limiting long-term illness	13.5
Education	Key stage 2-4 exam results, School absentee rates, Proportion of 18-19 year olds not entering higher education, Proportion of adults (25-59/64 year olds) with no qualifications	13.5
Housing and Geographical access to Services	Central heating, over-crowding and journey time to various resources	9.3
Living environment	Air quality and emissions, Flood risk and Proximity to refuse and industrial sites	5
Community Safety and Crime	Rates of burglary, theft, violent crime and criminal damage, Adult and youth offenders	9.3

Table 2: Patient demographics and clinical details

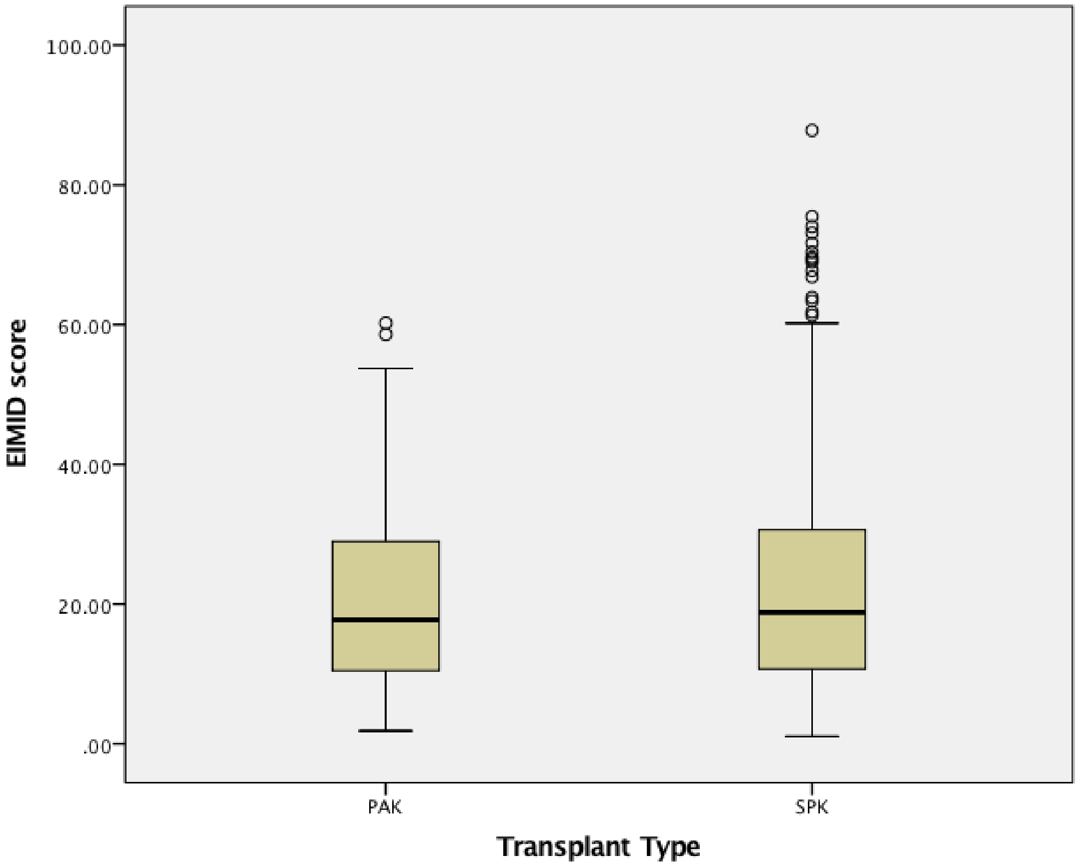
		Overall	Quartile 1 (Least deprived)	Quartile 2	Quartile 3	Quartile 4 (Most deprived)	p-value
Recipient median age in years (range)		42 (16-67)	42 (16–67)	43 (23-67)	42 (24-67)	41 (23–62)	0.15
Recipient gender	Male	743	157	182	212	192	0.0001
	Female	516	158	133	103	122	
HLA DR mismatch	0	145	41	38	32	34	0.9
	1	654	164	160	173	161	
	2	450	110	117	110	113	
Transplant Type	SPK	1017	251	251	256	259	0.9
	PTA	109	30	26	29	24	
	PAK	133	34	38	30	31	
Donor Type	DCD	191	47	54	45	45	0.72
	DBD	1068	268	261	315	314	
Donor median age in years (range)		37 (1-64)	38 (5–63)	36 (1-64)	37 (7-61)	37 (7–63)	0.76
Donor	Male	612	158	160	151	143	0.54

gender	Female	647	157	155	164	171	
Median Cold Ischaemic Time in minutes		755	720	741	733	752	0.59

Table 3: EIMD individual domain scores, with median, minimum, and maximum values

Domain	**Overall**	
	Median	**Range**
Income	0.12	0.01 – 0.77
Employment	0.09	0.01 – 0.75
Health	-0.01	-2.48 – 3.79
Education	17.9	0.18 – 89.39
Housing and Geographical access to services	20.48	0.73 – 70.14
Living environment	16.96	0.13 – 83.26
Community safety (crime)	0.1	-2.38 – 2.59

Figure 1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80.00
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EIMID score
PAK
SPK
Transplant Type

Figure 2:

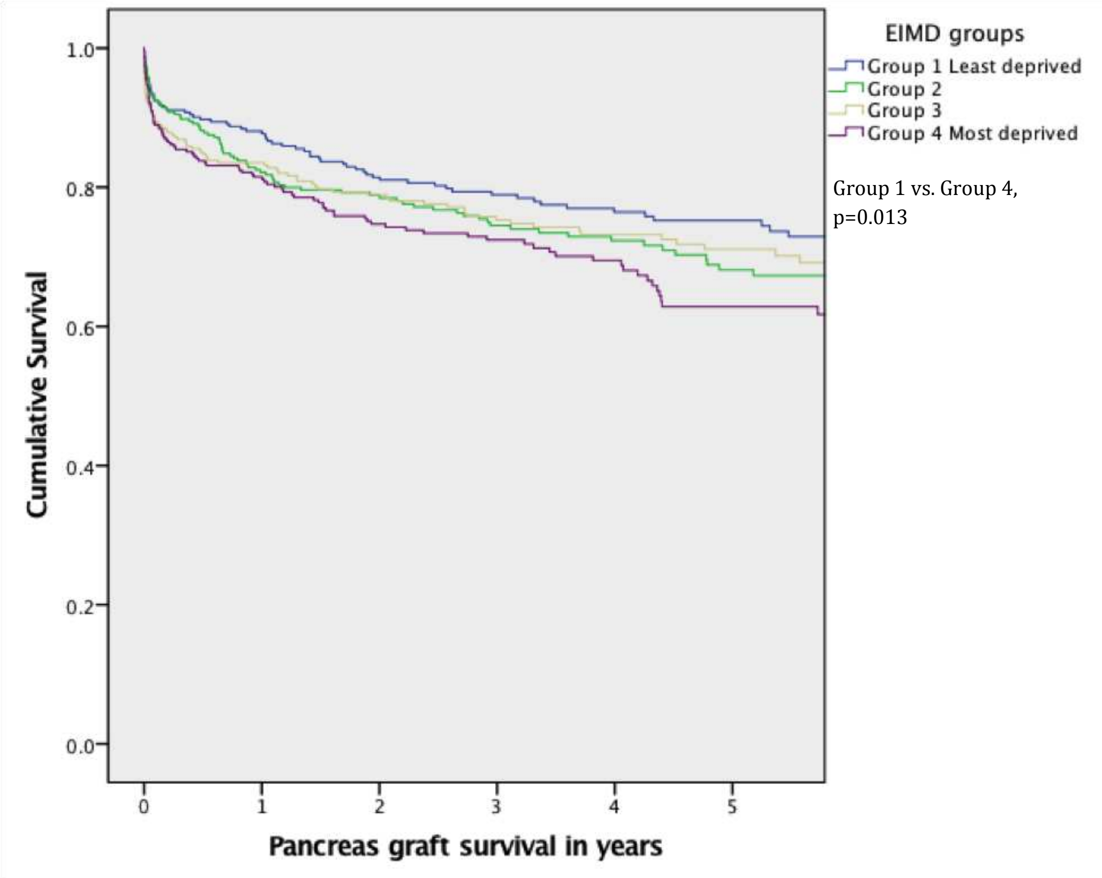
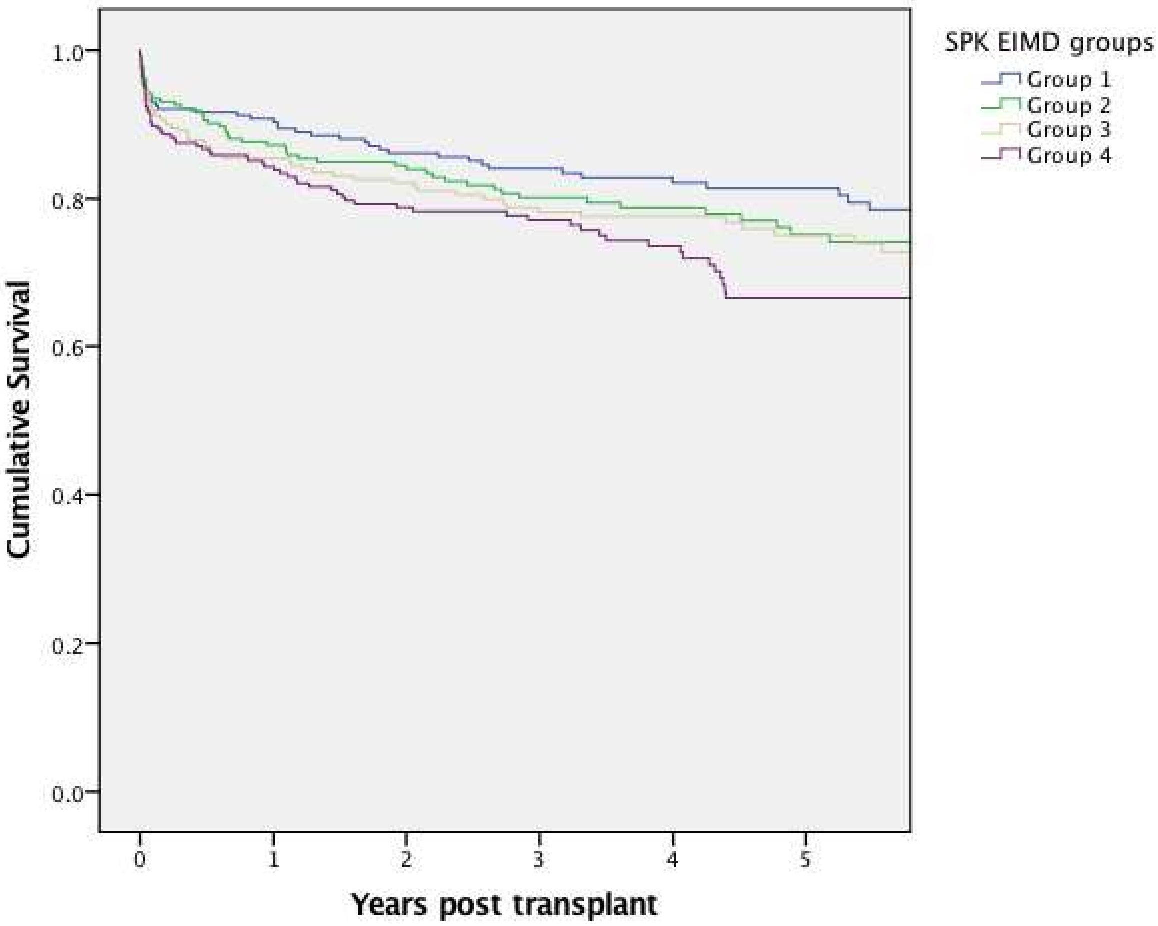

EIMD groups
Group 1 Least deprived
Group 2
Group 3
Group 4 Most deprived
Group 1 vs. Group 4,
p=0.013
1.0
0.8
0.6
0.4
0.2
0.0
Cumulative Survival
0
1
2
3
4
5
Pancreas graft survival in years

Figure 3:


SPK EIMD groups
Group 1
Group 2
Group 3
Group 4
Cumulative Survival
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0.8
0.6
0.4
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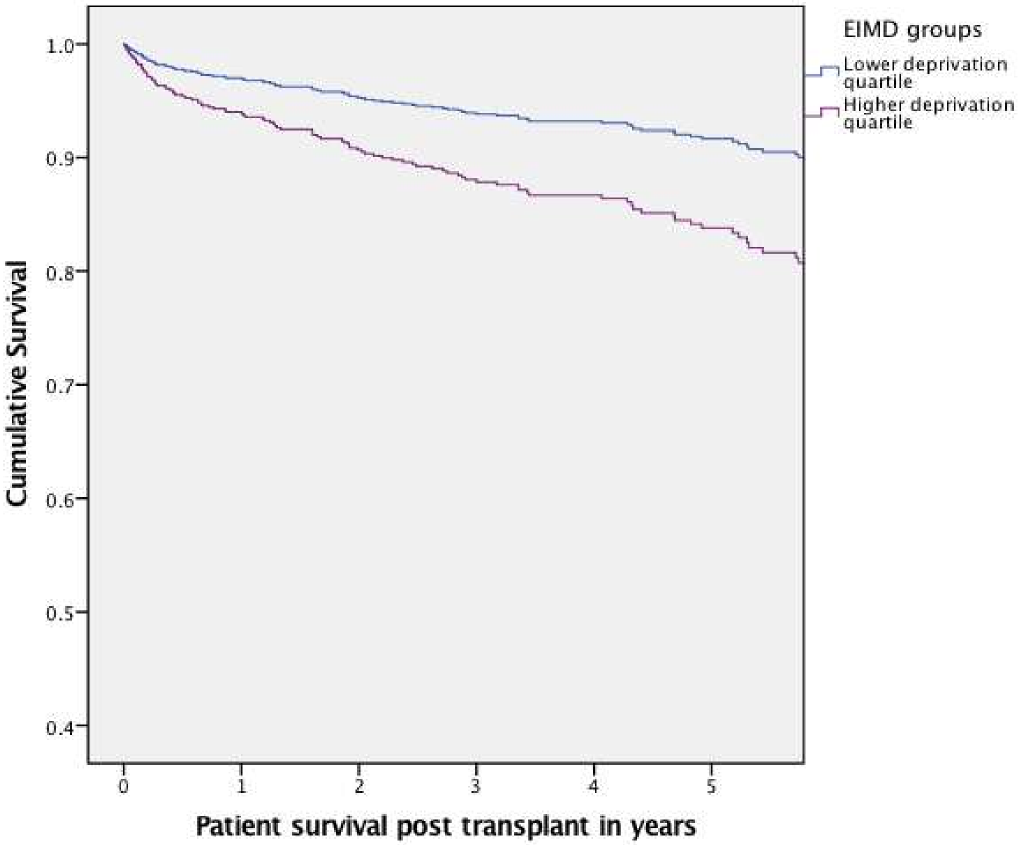
3
4
5
Years post transplant

Figure 4


EIMD groups
Lower deprivation quartile
Higher deprivation quartile
Cumulative Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
1
2
3
4
5
Patient survival post transplant in years